REMARKS

Claims 1 to 24 are present for purposes of prosecution.

Reconsideration of the rejection of this application is respectfully requested in view of the following remarks.

Claims 16 and 20 are objected to under 37 C.F.R. §1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim.

The fact that the formulation of the invention produces minimal irritation at the injection site is an important feature of the invention and further limits the subject matter of a previous claim (Claims 5 and 17). This feature is not an inherent feature but is a preferred limitation since the formulation as claims in Claims 5 and 17 may or may not have this feature. The previous Claims 5 and 17 do not require that the formulation claimed produces minimal irritation at the site of the injection. Accordingly, under these circumstances, it is submitted that Claims 16 and 20 are in compliance with 37 C.F.R. §1.75(c).

Claims 1, 4, 5, 7 to 10, 12, 13 and 16 are rejected under 35 U.S.C. §103(a) as being obvious over Parab et al. (U.S. 2002/0193438 A1).

The Examiner contends that Parab et al. teaches "that aripiprazole has limited aqueous solubility and suggests the use of solubilizing agents such as cyclodextrins."

Submitted herewith is a Declaration of Manoj Nerurkar and Vijay Naringrekar, two of the inventors of the subject matter claimed in the subject application, of prior invention to overcome U.S. 2002/0193438 A1 published December 19, 2002, filed on April 24, 2002 and claiming priority from Provisional application No. 60/286,718 filed on April 25, 2001.

Mark Dominick, the third inventor, did not have to sign the Declaration since he was not an inventor of the aripiprazole complexes claimed and set out in the lab notebook pages attached to the Declaration.

Also submitted herewith is a Declaration of Sunita Borsadia wherein she declares that she signed Manoj Nerurkar's notebook pages as a witness.

The enclosed Declaration of the inventors establishes reduction to practice of the invention claimed in the present application at a date prior to April 25, 2001, that is, the earliest effective date

of U.S. 2002/0193438 A1 (Parab et al.) (cited by the Examiner) as a reference, thereby removing U.S. 2002/0193438 A1 (Parab et al.) as a reference.

In view of the enclosed Declaration, it is submitted that Parab et al. should no longer be considered as a reference against the subject application and that the rejection based thereon should be withdrawn.

Claims 1 to 21 and 24 are rejected under 35 U.S.C. §103(a) as being obvious over Parab et al. (U.S. 2002/0193438 A1) in view of Rajewski et al. (J. Pharm. Sci. 1996).

As indicated above, the Parab et al. reference should be withdrawn as a reference leaving only Rajewski et al.

As the Examiner indicates, Rajewski et al. discloses "many varieties of cyclodextrins ... known for use for drug delivery."

However, there is no disclosure or suggestion in Rajewski et al. of an inclusion complex of aripiprazole in a substituted β-cyclodextrin. There is no disclosure or suggestion in Rajewski et al. of a formulation containing aripiprazole or of a formulation containing aripiprazole and a substituted β-cyclodextrin. Accordingly, it is clear that Applicants' invention as claimed is over Rajewski et al..

Claims 1 to 24 are rejected under 35 U.S.C. §103(a) as being obvious over Parab et al. (U.S. 2002/0193438 A1) in view of Rajewski et al. (J. Pharm. Sci. 1996) and further in view of Oshiro et al. (U.S. 5,006,528).

It is submitted that Applicants' invention as claimed is patentable over the above combination of references.

The Parab et al. reference is no longer applicable for the reasons mentioned above.

Rajewski et al. is discussed above and the comments there set out apply here as well.

The Examiner contends that:

> "OSHIRO teaches aripiprazole as a treatment for schizophrenia. See col 2, lines 38-40 and claim 12. The reference further teaches administration by a variety of routes, including intramuscular injection. See col 9, lines 16-29."

There is no disclosure or suggestion in Oshiro et al. of a complex of aripiprazole, and a β-cyclodextrin as claimed herein.

Oshiro et al. does not disclose or suggest employing aripiprazole with a β-cyclodextrin. Accordingly, Oshiro et al. adds nothing to Rajewski et al. which would make Applicants' invention

as claimed obvious. There is nothing in either reference which links aripiprazole to β-cyclodextrins or links β-cyclodextrins to aripiprazole. One skilled in the art reading either reference would have no reason to be motivated to try a cyclodextrin to improve solubility of aripiprazole. It could only be through the use of hindsight in view of Applicants' disclosure that one skilled in the art could ever suggest a complex of aripiprazole and a β-cyclodextrin.

In view of the foregoing, it is submitted that Applicants' invention as claimed is patentable over Rajewski et al. taken with Oshiro et al.

Claims 1 to 10, 13, and 15 to 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3 to 5, 18 or 19 of co-pending Application No. 10/131,304 in view of Rajewski et al. (J. Pharm. Sci. 1996).

The Examiner contends that:

> "The claims of '304 recite a pharmaceutical composition comprising aripiprazole in combination with a taste-masking agent and a buffer system. The claims do not include a cyclodextrin. However, it is known that cyclodextrins have that function in drug delivery. See RAJEWSKI at the section bridging pages 1154 and 1155 (sub-head 'Decrease of Local Tissue Irritation or Masking of Objectionable Taste'). It would have been obvious to modify the claims of '304 with any pharmaceutically acceptable taste-masking agent, such as cyclodextrins, thereby rendering the instant claims obvious over these co-pending ones.
>
> This is a provisional obviousness-type double patenting rejection. However, the application has been allowed but not yet issued. It is further noted that the allowed claims differ from the ones printed in the pre-grant publication (Parab et al.)"

It should first be pointed out that Parab et al. (U.S. 2002/0193438 A1) is the published form of application 10/131,304.

It is submitted that Applicants' invention as claimed is not obvious from the invention claimed in co-pending application 10/131,304 (Parab et al.) taken in view of Rajewski et al.

Application 10/131,304 includes allowed Claims 1, 3, 4, 5, 10, 11, 15 and 18 to 23.

The invention claimed in allowed Claim 1 of 10/131,304 is defined as a pharmaceutical solution which contains aripiprazole, a solvent system which is water, ethanol, glycerin, propyleneglycol and sorbitol, and one or more taste enhancing agents and one or more other agents which is lactic acid, acetic acid, tartaric acid or citric acid, which solution has a pH from 2.5 to 4.

Claims 3, 4, 5, 10, 11, 15, 22 and 23 of application 10/131,304 depend from Claim 1.

Claim 18 is essentially the same as Claim 1 except that the solvent system is not specifically defined and the other agent is defined as lactic acid.

Claims 19 and 20 depend from Claim 18.

Claim 25 defines a specific aripiprazole formulation.

Not a single allowed claim of 10/131,304 includes a cyclodextrin.

Applicants' inventive concept as claimed requires the presence of cyclodextrin in a complex with aripiprazole. Accordingly, it is clear that Applicants' invention is patentable over the claims of 10/131,304.

Rajewski et al. discloses that a cyclodextrin can be a solubilizing agent for a drug, but does not mention aripiprazole. However, there is no disclosure or suggestion in Rajewski et al. that a cyclodextrin could be or should be employed in conjunction with aripiprazole. As indicated at page 1149, left-hand column of Rajewski et al., last paragraph and continuing on to the right-hand column,

> "Only a limited number of studies have been performed to assess whether cyclodextrins can ameliorate the intrinsic irritancy of a drug after iv or im administration ... Svendsen 108 also demonstrated that β-CD could ameliorate the im irritancy of chlorpromazine, but not oxytetracycline hydrochloride...."

Thus, one skilled in the art reading Rajewski et al. would not know whether aripiprazole should be or could be used in a beneficial manner with a β-CD. Accordingly, absent the use of hindsight in view of Applicants' disclosure, it would not be obvious to one skilled in the art to use aripiprazole claimed in application 10/131,304 with a β-CD (as disclosed by Rajewski et al.) since there has not been sufficient studies reported to be able to generalize that β-CD can be used with any and all poorly water-soluble drugs. The Examiner is essentially basing the rejection on that it would be "obvious to try" aripiprazole and a β-CD. However, "obvious to try" is not a valid test for patentability. In re Jones (CAFC 1992) 21 USPQ 2d 1941.

A rejection based on the presumption that it would be "obvious to try" a β-cyclodextrin to increase solubility of aripiprazole by forming an inclusion complex therewith which is the very component that imparts novelty and patentability to the invention would not meet the requirement of 35 U.S.C. §103, that the issue of obviousness be based on the subject matter as a whole. There is nothing in either of the cited references that the inclusion complex of aripiprazole and a β-cyclodextrin should or could be prepared. The Examiner basically is maintaining that mere routine

experimentation is involved. However, the experimentation required is not within the teachings of the prior art. Neither cited reference discloses or suggests a complex of aripiprazole and a β-cyclodextrin. Furthermore, there is nothing in the cited prior art which would motivate one skilled in the art to use β-cyclodextrin with aripiprazole.

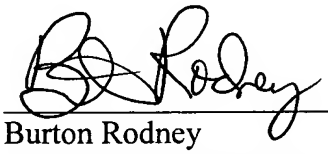
The Examiner cites pages 1154 and 1155 of Rajewski et al. which discloses that cyclodextrins and their derivatives may decrease local tissue irritation or mask objectionable taste. However, the decrease in local tissue irritation has to do with gastric lesions resulting from oral administration. As seen above, β-CD does not ameliorate im irritancy (at the site of the injection) with all drugs. There is nothing in the cited references which could lead one skilled in the art to try aripiprazole (disclosed in 10/131,304) out of the hundreds of compounds that are available, with a β-CD to improve solubility.

The combination of the claims of application 10/131,304 and Rajewski et al. does not disclose or suggest Applicants' invention as discussed above. Furthermore, there is nothing in either the claims of application 10/131,304 or the Rajewski et al. reference, not a teaching, a suggestion or incentive, which would suggest to one skilled in the art that such a combination should be made; obviousness cannot be based on such combination. In re Fine (CAFC 1988) 5 USPQ 2d 1596. There is nothing in either reference which makes it obvious that the teachings of these references should be combined. Accordingly, such a combination lacks basis, in fact, absent the use of hindsight in view of Applicants' disclosure and therefore is improper and should be withdrawn. In re Fitch (CAFC 1997) 23 USPQ 2d 1780, Ex parte Hiyamizu (BPAI 1988), 10 USPQ 2d 1393.

In view of the above, it is submitted that Claims 1 to 10, 13, and 15 to 21 are patentable over the claims of application 10/131,304 taken in view of Rajewski et al. It is therefore submitted that a terminal disclosure is not necessary in this case to overcome the combination of the claims of application 10/131,304 taken in view of Rajewski et al.

In view of the foregoing, it is believed that Claims 1 to 24 overcome all formal objections and are patentable over all cited references taken in any combination and therefore are in condition for allowance.

Respectfully submitted,



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